## Regulation of tooth number by fine-tuning levels of receptor-tyrosine kinase signaling.

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**Public Summary:**
Much of our knowledge about mammalian evolution comes from examination of dental fossils, because the highly calcified enamel that covers teeth causes them to be among the best-preserved organs. As mammals entered new ecological niches, many changes in tooth number occurred, presumably as adaptations to new diets. For example, in contrast to humans, who have two incisors in each dental quadrant, rodents only have one incisor per quadrant. In this paper, we studied a series of mice carrying mutations in genes encoding signaling antagonists. Our findings indicate that altering genetic dosage of an antagonist can recapitulate ancestral dental characters, and that tooth number can be progressively regulated by changing levels of activity of a single signal transduction pathway.

**Scientific Abstract:**
Much of our knowledge about mammalian evolution comes from examination of dental fossils, because the highly calcified enamel that covers teeth causes them to be among the best-preserved organs. As mammals entered new ecological niches, many changes in tooth number occurred, presumably as adaptations to new diets. For example, in contrast to humans, who have two incisors in each dental quadrant, rodents only have one incisor per quadrant. The rodent incisor, because of its unusual morphogenesis and remarkable stem cell-based continuous growth, presents a quandary for evolutionary biologists, as its origin in the fossil record is difficult to trace, and the genetic regulation of incisor number remains a largely open question. Here, we studied a series of mice carrying mutations in sprouty genes, the protein products of which are antagonists of receptor-tyrosine kinase signaling. In sprouty loss-of-function mutants, splitting of gene expression domains and reduced apoptosis was associated with subdivision of the incisor primordium and a multiplication of its stem cell-containing regions. Interestingly, changes in sprouty gene dosage led to a graded change in incisor number, with progressive decreases in sprouty dosage leading to increasing numbers of teeth. Moreover, the independent development of two incisors in mutants with large decreases in sprouty dosage mimicked the likely condition of rodent ancestors. Together, our findings indicate that altering genetic dosage of an antagonist can recapitulate ancestral dental characters, and that tooth number can be progressively regulated by changing levels of activity of a single signal transduction pathway.